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The Relationships of Benign Lesions of the Breast to Cancer* †

ARTHUR PURDY STOUT, M.D.

Emeritus Professor of Surgery,
College of Physicians and Surgeons, Columbia University

IN 1947 the Journal of the National Medical Association was kind enough to publish an article by me dealing with certain aspects of cancer and other diseases of the female mammary gland.[1] It seems worth while to supplement that paper by discussing one phase neglected at that time, namely, the relationship of benign lesions of the breast to cancer. There are two features of paramount importance. In the first place it is always necessary to realize that a number of benign lesions can give the cardinal physical signs of cancer and conversely, there are cancers which can so closely simulate the physical signs of benign tumors and cysts as to be mistaken for them. The second relationship concerns the question as to whether any of the benign lesions of the breast are precancerous in the sense that breast cancer is more likely to develop in them than in the breasts of other women of comparable age. If the answer is yes, what action if any should be taken to prevent the development of cancer?

BENIGN LESIONS CLINICALLY SIMULATING CANCER

I think that all who have had experience with breast lesions will agree that there are some benign conditions which can produce the signs of cancer. In fact at times almost any of the benign lesions mentioned in Table 1 can do so. I should like to emphasize certain ones especially. *Fat necrosis* which can occur without remembered trauma often leads to the formation of an irregular cystic space filled with oily or hemorrhagic fluid or a mixture of the two. The fibrous granulomatous tissue which surrounds the cyst is firmly attached to the fibrous septa which divide the mammary gland and attach it to the skin. Contraction of the granulation tissue pulls upon these septa and produces a dimpling of the overlying skin. The palpating hand in such a case feels a hard nodule attached to the surrounding breast tissue which when moved accentuates the dimple in the skin. If there is no history of trauma and no ecchymosis, the imitation of carcinoma is flawless (Adair and Munzer[2]).

The peculiar condition known variously as *mammary duct ectasia* (Haagensen[3]) comedomastitis (Tice et al.[4]), plasma cell mastitis (Adair[5]) and mastitis obliterans (Payne et al[6]) results from the accumulation in some of the ducts in the zone of the areola of a substance rich in cholesterol and lipids which is very irritating. As a result the sheaths of the ducts become thickened and fibrous and if the material in the ducts escapes into the surrounding breast parenchyma it occasions a sharp inflammation with infiltration

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† From the Surgical Pathology Laboratory, Columbia University and the Pathology Laboratory, Francis Delafield Hospital, N. Y.

TABLE 1—NEOPLASMS AND TUMOR FORMING LESIONS OF THE BREAST

Benign		*Malignant*
Adenofibroma	Lipoma	Carcinoma
Simple intracanalic	Leiomyoma	Circumscribed
Giant intracanalic.	Gran. cell myoblastoma	(medullary)
(Benign cystosarcoma phyllodes)	Hemangioma	Papillary
Adenosis (fibroadenosis)	Hemangiopericytoma	Intraductal
Cystic disease (fibroadenomatosis)	Lymphangioma	Paget's disease
Fibrous disease	Fat necrosis	Malignant cystosarcoma phyllodes
Intraductal papilloma	Duct ectasia	Fibrosarcoma
Mixed tumor	(Comedomastitis)	Liposarcoma
	(Plasma cell mastitis)	Rhabdomyosarcoma
		Malig. hemangioendothelioma
		Lymphosarcoma
		Hodgkin's disease
		Malig. mixed tumor

of a variety of cells, including plasma cells and histiocytes. This zone of inflammation forms a hard nodule of indistinct outlines in the breast and dislocates the thickened ducts so that the nipple may be retracted or displaced and a dimple may be formed in or near the areola. Since all this takes place painlessly, again there is a perfect simulation of a breast cancer.

A rare simulator of a cancer nodule in the breast is the tumor known as *granular cell myoblastoma* (Haagensen and Stout[7]). This produces a hard circumscribed non-encapsulated nodule which sends short prolongations into the fibrous septa that compartmentalize the mammary gland and are attached to the skin. The attachments contract and a dimple forms in the skin covering the mammary gland.

A somewhat different situation exists in regard to the rather uncommon tumor known as *cystosarcoma phyllodes*. The most spectacular feature of this neoplasm is growth to a large and occasionally a gigantic size, although this is not always manifest. It has the multinodular form and hardness of an adenofibroma, usually of the intracanalicular variety, but instead of the fibrous stroma of the ordinary tumors bearing these names, one or more parts of the stroma assume the aspect of either a fibrosarcoma or a liposarcoma. It has usually been considered as a malignant tumor probably because the word sarcoma is included in the name given to it by Johannes Müller in 1838 and also because of its spectacular size. Treves and Sunderland[8] have established that the name is justified because sometimes the tumor metastasizes through the blood stream as a sarcoma but never as a carcinoma or carcinosarcoma. But as pointed out by Lester and Stout[9] the metastatic rate among the thirty-six cases treated at the Presbyterian Hospital was only one case or 2.8 per cent. It is of interest to note that that one case came at the end of the period of thirty-nine years during which the cases were being collected. Unfortunately it is impossible to recognize the cases of cystosarcoma phyllodes which will metastasize on the basis of their histological characteristics. But we have been convinced that any form of operation which will remove all of the local tumor will be as effective as a radical mastectomy which is probably never necessary. Whether or not a fibroepithelial tumor of the breast should be regarded as more apt to give rise to a metastasizing sarcoma than breast stroma not connected with such a tumor is very hard to determine. The incidence of metastasizing cystosarcoma phyllodes among all fibroepithelial tumors removed at the Presbyterian Hospital was one in 1436 or 0.0007 per cent. In all the rest of the breasts surgically removed and not associated with fibroepithelial tumors there were only two sarcomas which were known to have produced metastases. It is impossible to believe that there is any significant difference between these two figures no matter how many breasts are concerned so that it seems impossible to suggest that fibroepithelial tumors in the breast are any more likely to produce sarcomas that metastasize than is the ordinary breast stroma.

The next and by far the most important item for discussion is the relationship of *cystic disease* and its associated proliferative phases. It should always be remembered that this condition, while often accentuated in one breast so as to become

clinically apparent, is almost always bilateral. The writer feels that the proliferative phases of cystic disease include the fibroadenomas, intraductal papillomas and adenosis. But as many of these lesions may be clinically distinct from cystic disease with gross cysts, they will be discussed separately.

Fibroadenomas can simulate carcinoma by becoming hard and fixed to surrounding mammary tissue. They may even be calcified. They are especially confusing when they become manifest after the menopause. An unusual imitator of localized cystic disease is called by Haagensen *fibrous disease.* This is found occasionally usually in women before the menopause. It consists of a localized area of fibrous thickening in one or both breasts which can form a palpable nodule of uncertain character demanding investigation. It is entirely harmless except for the clinical uncertainty occasioned by its presence. In like manner a localized area of acinar proliferation called *adenosis* may be indistinguishable from the feel of a carcinoma whether or not it is associated with fibrous, microcyst formation or intraductal hyperplasia. Indeed any other phase of *cystic disease* whether it be a simple *cyst,* a group of cysts with or without intraductal hyperplasia or a gross *intraductal papilloma* can produce a palpable nodule which cannot with absolute assurance be distinguished from a carcinoma. When these various fibrous and fibroadenomatous lesions produce a lump in the breast of different consistency from all the rest of the mammary tissues, whether nodular or not, it is probably described as a dominant lump and becomes suspect no matter how sure the experienced surgeon may be that the lesion is benign. The reason for this is very simple. Not every carcinoma gives the cardinal signs of fixation to surrounding mammary tissues and retraction producing skin dimpling and nipple distortion. Some breast carcinomas are quite sharply circumscribed so that they seem as freely movable as are cysts. It is for these reasons that any dominant lump in the breast should be investigated by biopsy before treatment is undertaken. If suspected clinically of being benign it may turn out to be a cancer and to neglect it as harmless will probably condemn the woman to death. On the other hand, while most lesions that give the cardinal signs of breast carcinoma are such, not all of them are and to do a radical operation without microscopic proof of malignancy is to subject the woman to needless sacrifice of tissue and anxiety of mind.

It is beyond the scope of this paper to discuss the minute changes with which the pathologist must struggle in deciding whether certain extreme intraductal and acinar proliferations are or are not carcinoma. He will only say that a pathologist needs to have a considerable amount of experience to distinguish between the two. The writer suspects that a certain number of radical mastectomies are done for lesions that are hyperplasias and not carcinoma and conversely that occasionally a diagnosis of intraductal carcinoma is missed because of insufficient experience on the part of some pathologists.

THE SO-CALLED "PRECANCEROUS" LESIONS

The next subject for discussion concerns the non-physiological mammary epithelial hyperplasias and whether or not they are to be regarded as significant precancerous lesions. The opinions expressed about them are nearly unanimously that a cancer is more likely to develop from such epithelium than from non-hyperplastic duct epithelium, but the evidence that this is so does not have a firm foundation. There are some suggestive data but I believe that the majority of those who have investigated the subject have been influenced consciously or unconsciously by the fact that in a number of mucosal surfaces in other parts of the body and in the skin there occur indubitable precancerous changes and carcinoma *in situ* which have been proved beyond question to be followed by invasive cancer. One thing which the oncologist must learn, for it is axiomatic, is that changes of a morphological character which are observed in one organ or body surface and which seem similar to or even identical with those in another, are not by any means necessary comparable biologically for they may behave in a quite different fashion. Further the coincidence of carcinoma cells in a duct or acinus which also shows evidences of benign hyperplasia is no proof that the carcinoma arose from such hyperplastic cells, for it is well-known that mammary carcinoma can extend along ducts and into or away from acini remote from the actual starting focus.

There is one phase of generalized cystic disease with hyperplasia which should be discussed

separately from the disease as a whole because it poses a special problem of treatment. Much of the intraductal hyperplasia associated with cystic disease is of a papillary or cribriform variety but of microscopic proportions so that its existence cannot be detected clinically. Occasionally, however, it reaches macroscopic proportions and involves especially the ducts in the vicinity of the areola and is usually palpable. It is then called *intraductal* or *intracystic* papilloma. Usually the lesion is confined to a few ducts near the areola but occasionally there may be several macroscopic papillary cysts in more than one quadrant of the breast. When near the nipple these papillomas are associated with a discharge from the nipple which may be bloody in 85 per cent of cases. When not near the nipple only 35 per cent have a nipple discharge. It seems worth stressing the fact that excluding cases of obvious late cancer, a discharge from the nipple is rarely an early sign of cancer of the breast. Haagensen, Stout and Phillips[10] put it at 1.3 per cent and Hollenberg[11] found a bloody discharge in only 1 per cent of private patients with breast cancer coming to his office for examination.

The majority of observers believe that intraductal papillomas are benign tumors (Hollenberg,[11] Chester and Bell,[12] Estes and Phillips,[13] Haagensen, Stout and Phillips[10]): Saphir and Parker[14] believe that most papillomas are benign but that there is a transitional cell papilloma which is precancerous. Abramson and Tucker[15] feel that when papillomas are multiple in the breast they may be precancerous or actually true carcinomas, Hollenberg,[11] Chester and Bell[12] and the surgeons who discussed their papers were all fearful of multiple scattered papillomas and were quite willing to do simple mastectomies for them. Semb[16] was so sure that intraductal papillomas are malignant tumors that he advocated radical mastectomy for the condition.

Why are all these gentlemen so sure that intraductal papillomas of the breast of macroscopic proportions are precancerous tumors? Some will tell you that cancer cells have been found associated with benign intraductal papillomas. I have been looking at sections of breast lesions ever since I was a second year medical student 45 years ago and during all that time I have seen only once the presence of true cancer cells in a duct papilloma in such an arrangement as to suggest that the carcinoma might have developed from the papilloma. In three other cases there was a benign intraductal papilloma in the nipple zone and an unrelated carcinoma in another part of the same breast. Most attempts to determine the incidence of cancer development from intraductal papillomas by follow-up studies are fruitless because when discovered the papilloma is removed. All that can then be demonstrated is that local removal of the papillomas and surrounding tissue in the affected quadrant is a safe procedure because the rate of breast cancer development in either breast following it is no higher than the expected breast cancer development rate for a comparable age group and period of time. Haagensen, Stout and Phillips[10] followed sixty-nine women treated by local excision for a maximum period of five years and twenty-seven of these for ten or more years. Not one developed a cancer of either breast during this period of observation. It was therefore concluded that the procedure was a justifiable one.

I suspect that part of the bad name which clings to the intraductal papilloma comes from the fact that there are such things as papillary intraductal carcinomas and while these are less malignant as a group than the commoner forms of breast carcinoma, they are true carcinomas and so far as I have been able to observe unrelated to benign intraductal carcinoma. If a lesion is a carcinoma and falls into the operable class, in my opinion it should be treated by radical mastectomy. A generous local excision will suffice for all solitary tumors or multiple tumors limited to one breast quadrant. A simple mastectomy may be proper for multiple benign mascroscopic papillomas scattered throughout an entire breast but such cases undoubtedly are very rare. As far as I am concerned there exists no proof that the intraductal breast papilloma should be classified as a precancerous lesion.

If cancer development is rarely proved in intraductal papillomas, it is just as rare in fibroadenomas of the breast. I had to wait forty-five years until 1954 before I saw a case of intracanalicular fibroadenoma, the epithelial cells of which had become definitely carcinomatous. Before that I had seen two instances in which a carcinoma had invaded an intracanalicular fibroadenoma because it happened to lie within the field of cancer

invasion but never one in which the benign epithelial cells had become cancerous.

Finally we come to the highly controversial subject of the relationship of *cystic disease* to cancer of the breast.[17, 18] The literature on this subject, already voluminous, is growing. It is confusing to read because the majority of writers are willing to accept both factual and statistical evidence as proof, which in my estimation is not free from the suspicion of inaccuracy. I hasten to say that I do not have the answer as to the exact relationship between cancer and cystic disease but I shall try to set forth the data and my reaction to it.

Most of the authors referred to in the bibliography who have written about the relationship are convinced that the expectation of breast cancer development is greater in a group of women with cystic disease of the breast than is the expected cancer development rate in the female population of comparable age. (Clagett, Plimpton and Root,[19] Cole and Rossiter,[20] Cutler,[21] Dawson,[22] Geschickter,[23] Logie,[24] Lewison and Lyons,[25] McKinley[26] Semb,[16] Slaughter and Peterson,[27] and Warren[28]).

The reasons for so thinking are the following. It has been shown by Semb[16], Foote and Stewart[29], Oberhelman[30], and the writer* that the incidence of cystic disease of all types in breasts with carcinoma is from 50 to 82.4 per cent. The exact incidence of cystic disease in adult women of comparable age is unknown. The nearest approximation stems from the study of autopsy breasts of women dying without known disease of that organ conducted by Frantz and her associates[31]. They found the incidence of cystic disease to be 52 per cent. This difference is interesting but, of course, proves nothing. A good many pathologists have described cancer cells intermingled with ducts or acini showing proliferative changes and have suggested that this means the cancer cells were derived from these proliferated cells. But this cannot be accepted as proof for no one has seen the actual start of breast cancer from a single focus so that the observations in question can be interpreted as evidence of spread with greater probability than as proof of *in situ* derivation.

The only sure way of determining the actual incidence of carcinoma development in women with cystic disease is to take a large group of them in whom the diagnosis has been determined by local excision of an involved portion of the breast and follow them for the rest of their lives noting the number that develop breast cancer. Since this would mean a follow-up period of 30 or 40 years without any losses to follow-up and an autopsy after death at which all cases not already known to have breast cancer have a thorough investigation of both breasts, it has never been done and probably never will be. As an alternative, groups of women known to have cystic disease and not treated by total mastectomy have been followed for periods averaging ten years more or less and the cancer development rate compared with various estimated breast cancer development rates in the population with due allowance for the fact that the women under investigation have only been followed for limited periods of time. When this has been done in the past authors like Warren (1940),[32] Clagett et all[19] and others have estimated that the breast cancer development rate in women with cystic disease is 4.5 to 5 times greater than the expected rate in the female population of comparable age. The most recent and most enlightened study of this nature is by Lewison and Lyons[25]. They followed a group of 385 women with benign breast diseases for an average of 13.6 years. During that period seven cancers developed, an incidence of 1.8 per cent. Of this number there were 153 women on whom the diagnosis of chronic cystic mastitis was made—four of these women developed cancer—an incidence of 2.6 per cent. The average age of these women was forty-two years.

In order to have some figure with which to compare this one, the authors have had to use statistical tables of expected breast cancer development rate for various age periods based on the vital statistics of the United States. When this was done by Lewison and Lyons the rate was 2.6 to 3.6 times as great as the expected rate depending upon the method of calculation used. These figures are undeniably impressive but it is interesting to find that this rate is less than the earlier estimations of Warren and Clagett et al. The writer is not yet ready to accept the reported increased rate as settled until the actual breast cancer development rate in the female population is upon a firmer basis. The figures of expected breast cancer development rate for life of females in New York State outside of New York City

* Unpublished data.

at age thirty is 3.7 per cent according to Levin[33]. The writer would like to feel certain that the breast cancer development rate in women with cystic disease for life is significantly higher than this figure before he is convinced that cystic disease of the breast can truly be regarded as a real precancerous lesion. In any event those who contemplate simple mastectomy as a prophylactic measure to prevent cancer of the breast should take note of the fact reported by Lewison and Lyons that four of the seven cancers which developed in their series were found in the non-operated breast. It must also be remembered that the usual simple mastectomy never removes all of the outlying portions of breast tissue on the operated side. A simple mastectomy as a prophylactic for cancer of the breast is a delusion.

The writer does not wish to leave the impression that he does not believe that cystic disease with hyperplasia does not provide a more favorable condition for the development of cancer of the breast than its absence. He simply wishes to indicate that he has not yet been offered proof convincing to him that this is so. Under certain circumstances the relationship is definite. Morse,[34] Smithers[35] and others have shown that women with cancer of the breast give a history of a mother with breast cancer three times as often as might be expected for women of comparable age in the general population and Lewison and Allen[36] made the following interesting observation. In three groups of women, the group without evidence of breast disease gave a family history of breast cancer in 1.9 per cent; a second group with evidence of benign breast disease showed a family history of breast cancer in 5.5 per cent and a third group with breast cancer had a family history of breast cancer in 9.1 per cent. In the case reported by Auchincloss and Haagensen[37] a woman with a marked familial breast cancer history who was treated for about a year with large doses of estrogenic hormone had widespread proliferative cystic disease and what was interpreted as multicentric cancer. A small number of comparable cases have since been reported. It would be easy to interpret these findings as evidence in favor of a possible sequential relationship between proliferative cystic disease and cancer yet actually they do not prove anything of the sort for they are susceptible of other interpretations.

SUMMARY

It has been indicated that there are a number of benign lesions of the breast including especially fat necrosis, mammary duct ectasia and granular cell myoblastoma which can give the clinical signs of breast cancer and there are occasional breast cancers which clinically simulate benign lesions. There are many other lesions which clinically are indeterminate. These facts serve to underline the importance of the biopsy before treatment of a dominant lump in the breast. The peculiar fibroepithelial tumor of the breast with sarcoma-like proliferation in its stroma called cystosarcoma phyllodes is a metastasizing tumor very rarely and complete local excision serves to cure all but 2.6 per cent of cases. The macroscopic intraductal papilloma is a benign tumor and there is no proof that it gives rise to cancer at a higher rate than the expected one in the female population. There does not seem to be any relationship between papillomas and papillary intraductal carcinomas. If all of the data upon which the figures are based are reliable, cancer develops in the breasts of women with proved cystic disease from 2.5 to 5 times more often than it does in the breasts of the female population. But the writer is not yet willing to accept all the data as necessarily accurate and in his opinion the relationship is not definitely established. For this reason and because cystic disease is probably always bilateral, simple unilateral mastectomy as a prophylactic procedure for the prevention of breast cancer is an ineffectual one.

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